Remarks

Claims 27-38, 45-50, 57-62 and 81-86 are pending in the application, with claims 27, 33, 45, 57 and 81 being the independent claims.

The present application is a divisional of U.S. Application No. 08/741,095, filed October 30, 1996, and claims the benefit of the filing dates of International Application No. PCT/US95/05058 (the '058 application), filed April 27, 1995, and U.S. Application Nos. 08/464,595 (the '595 application), 08/462,962 (the '962 application), and 08/462,315 (the '315 application), each of which was filed June 5, 1995. In addition, all of the above noted applications are incorporated by reference into the present application.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Status of Application, Amendments and/or Claims

The Examiner indicated that the Reply filed August 30, 2001 has been entered and that claims 27-38, 45-50, 57-62 and 81-86 are pending in the instant application and are under examination. (*See* Paper No. 16, page 2.)

Withdrawn Objections and/or Rejections

Applicants thank the Examiner for the withdrawal of the objection under 35 U.S.C. § 132 to the amendment filed on June 29, 1999, regarding new matter and for the withdrawal

of the rejection of claims 27-32 and 81-86 under 35 U.S.C. § 112, first paragraph, regarding inadequate written description. (*See* Paper No. 38, pages 2-3.)

The Telephone Interview

Applicants' representative wishes to thank Examiner Kemmerer for the helpful and courteous telephone interview of January 15, 2002. As a result of the discussion, it is believed that the issues in the case have been clarified and that the prosecution of the application has been materially advanced. In particular, it is believed that the Examiner's apparent misunderstanding of the differences between SEQ ID NO:2 and SEQ ID NO:26 has now been clarified.

Rejections under 35 U.S.C. §§ 101 and 112, First Paragraph

The Examiner maintained the rejection of claims 27-38, 45-50, 57-62 and 81-86 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility. (*See* Paper No. 16, page 3.) Applicants respectfully traverse this rejection.

The specification discloses several statements that specifically set forth Applicants' assertions of the TR2 receptor's biological role and explain why the Applicants believe the invention is useful. In general, the "invention relates to TNF receptor, the amino acid sequence of which is set forth in SEQ ID NO:2." (The '058 application, page 6, lines 24-25.) In addition, "[t]he TNF receptor and the two splice variants belong to a family of receptors and antigens known as the Nerve Growth Factor/Tumor Necrosis Factor Family." (The '058 application, page 4, lines 1-3.) As disclosed in the '058 application at page 7, lines 16-17,

the TR2 receptor "is structurally related to the human NGF/TNF receptor family." (The '058 application, page 7, lines 12-17.)

In particular, "[t]he receptor polypeptides of the present invention show significant amino acid sequence homology to the type 2 human tumor necrosis factor receptor." (The '058 application, page 4, lines 13-16; *see also* Figure 2.) In fact, "[t]he protein exhibits the highest degree of homology to a human type 2 TNF receptor with 32% identity and 44% similarity over a 117 amino acid stretch." (The '058 application, page 7, lines 21-23.) Moreover, the type 2 TNF receptor is known "to exclusively mediate human T cell proliferation by TNF as shown in PCT Publication No. WO 94/09137." (The '058 application, page 3, lines 24-26.)

Accordingly, it was asserted in the specification that the TR2 polypeptide of the present invention has biological effects and activities similar to type 2 TNF receptor. For example, it is asserted that within the scope of the invention there are provided processes of using "agonists for treating conditions related to insufficient activity of the polypeptide of the present invention, for example, . . . to stimulate human cellular proliferation, e.g., T-cell proliferation, . . . and to treat immunodeficiencies such as is found in HIV." (The '058 application, page 5, lines 13-20; *see also* the '058 application at page 20, line 25, to page 21, line 6 and page 26, lines19-21.) Further, it is asserted in the '058 application that "[a]ntagonists to the receptor polypeptides of the present invention may be employed to treat autoimmune diseases, for example, . . . T-cell mediated autoimmune diseases such as AIDS. It has been shown that T-cell proliferation is stimulated via a type 2 TNF receptor. Accordingly, antagonizing the receptor may prevent the proliferation of T-cells and treat T-cell mediated autoimmune diseases." (The '058 application, page 27, lines 1-5.)

In view of the above, Applicants submit that the assertion that the claimed receptor can stimulate T cell proliferation and would be useful to treat immunodeficiency-related diseases by increasing the rate of lymphocyte proliferation and differentiation is not only specific and substantial, but credible as well. However, the Examiner is of the opinion that the TR2 receptor of the present invention and the type 2 TNF receptor do not possess this same functional property. (*See* Paper No. 16, pages 3-7.) In particular, the Examiner contends that

> the art acknowledges that TNF receptors mediate diverse and even opposite effects. The specification also acknowledges this at pp. 73-74. In general, the art acknowledges that structural similarity among gene family members, such as growth factor, hormone or receptor families, cannot be relied upon for prediction of functional similarity.

(Paper No. 16, page 4.) The Examiner further asserted that "the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases." (Paper No. 16, page 5.)

Although the Examiner is skeptical of the predictability of homology-based assertions of utility, this skepticism is irrelevant in view of the fact that the asserted activity has been demonstrated to be true. The data presented in the instant application in Example 6, as well as in the Kwon *et al.* and Harrop *et al.* references, *confirm* that the presently claimed TR2 receptor is involved in T cell proliferation, thereby rendering the Examiner's homology-based arguments moot.

According to the Examiner, however,

> [t]his is not found to be persuasive, because Example 6, Kwon et al. and Harrop et al. pertain to the activities of the receptor of SEQ ID NO:2, not the instantly claimed SEQ ID NO:26. As reviewed above, one cannot infer functional similarity among structurally similar TNF receptors, based on

> evidence in the art that the members of the TNF receptor family have diverse and even opposite activities.

(Paper No. 16, page 7.) Applicants respectfully assert that this proposition is incorrect in view of the fact that the polypeptides of SEQ ID NO:2 and SEQ ID NO:26 are both in fact TR2 receptors according to the invention. Out of a possible 283 amino acids, the two proteins *differ by only one amino acid.*

As disclosed in the specification,

> [t]he TR2 receptors of the present invention include several allelic variants containing alterations in at least these three nucleotides and two amino acids. Nucleotide sequence variants which have been identified include either guanine or adenine at nucleotide 314, thymine or cytosine at nucleotide 386,and thymine or cytosine at nucleotide 627 shown in FIG. 1A-1B (SEQ ID NO:1). While the identified alteration at nucleotide 627 is silent, the alteration at nucleotide 386 results in the codon at nucleotides 385-387 encoding either serine or phenylalanine and the alteration at nucleotide 314 results in the codon at nucleotides 313-315 encoding either lysine or arginine.

(Specification, page 9, lines 20-28.) It is the latter alteration, *i.e.*, the codon at nucleotides 313-315 encodes for lysine in SEQ ID NO:2 and arginine in SEQ ID NO:26, which accounts for the only difference in the amino acid sequence between the two polypeptides. As such, the two polypeptides are merely *allelic variants of the same protein.* Moreover, the alteration occurs in the signal sequence of the TR2 receptor. This sequence is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated and is not directly involved in protein function.[1]

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[1]It should be noted that "in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that the cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide." (Specification, page 15, lines 14-18.)

In view of the above, one skilled in the art can confidently infer functional similarity among the nearly structurally identical TR2 receptors, especially in view of the fact that they differ only in one amino acid residue located in the signal sequence. In addition, Applicants point out that if a specific and substantial utility is asserted in the specification, a post-filing date reference setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. . . . It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility)." *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995). Accordingly, a biological activity of the claimed TR2 receptor of SEQ ID NO:26 has been demonstrated, *i.e.*, as an inducer of T lymphocyte proliferation and differentiation.

Applicants note that the manner of making and using an invention disclosed in a specification must be accepted by the PTO "unless there is reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 439 F.2d 220, 223, (CCPA 1971). Any doubt the Examiner may have had with respect to the truth of the utility statements should be obviated in view of the confirmatory data.

In addition, a *prima facie* showing of no specific and substantial utility "must establish that it is *more likely than not* that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02(III.)(A.) at 2100-39 (Eighth edition, August 2001) (emphasis added). Even assuming, *arguendo*, the Examiner has established a *prima facie* showing that the claimed invention lacks utility, Applicants respectfully submit that the evidence of record would be sufficient to lead one skilled in the art to conclude not only that the asserted utility is more likely than not true, *but that it is in fact true*, and would be sufficient to rebut the Examiner's showing. As such, Applicants

respectfully submit that the presently claimed invention possesses a specific, substantial and credible utility that constitutes a patentable utility under 35 U.S.C. § 101. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 27-38, 45-50, 57-62 and 81-86 under 35 U.S.C. § 101.

The Examiner further maintained the rejection of claims 27-38, 45-50, 57-62 and 81-86 under 35 U.S.C. § 112, first paragraph. (*See* Paper No. 16, page 3.) Specifically, it is the Examiner's contention that "since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (*Id.*)

For the reasons discussed above in response to the rejection under 35 U.S.C. § 101, the claimed invention is supported by at least one specific, substantial and credible utility. Since the Examiner "should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. 101 rejection is proper" (M.P.E.P. § 2107.01 (IV) at 2100-36 (Eighth edition, August 2001)) and the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility of the claimed invention, should be withdrawn.

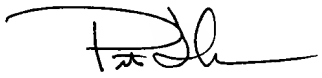
Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Peter A. Jackman
Attorney for Applicants
Registration No. 45,986

Date: Jan 22, 2002

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600